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Essential Pentosuria.

BY

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The Chemical Examination of a Sample of Urine Containing Pentose.

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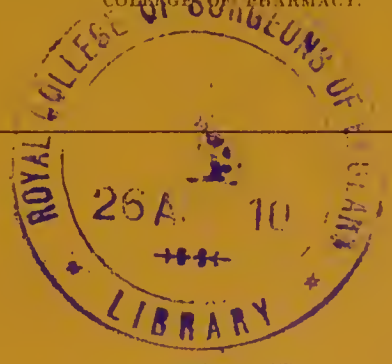

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ESSENTIAL PENTOSURIA.[1]

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The old dictum that life is the chemistry of carbon receives additional illustration in the anomalous condition known as pentosuria—the presence in the urine of the pentatomic form of sugar. It constitutes as yet little more than a clinical curiosity, but suggests many important questions, whose answers, when found, will doubtless be illuminating as to certain dark corners of the field of metabolism.

Pentose is a species name rather than an individual designation. It is applied to a group of some eleven monosaccharids, having the general formula $C_5H_{10}O_5$, and thus differing, by one carbon atom and the elements of a molecule of water, from dextrose, levulose, galactose, etc., which, containing six carbon atoms in the molecule, are termed hexoses. But this apparently slight chemical difference is of considerable physiological and pathological importance. The sugar which appears in the urine in diabetes mellitus is dextrose; and, as we all know, its presence usually indicates a profound and often dangerous disorder of metabolism, associated with distressing symptoms and having a somewhat uncertain dependence upon more or less definite structural lesions. While hexosuria is thus potentially and often actually grave, pentosuria, on the other hand, is essentially mild. It is unaccompanied with the polyuria, polydipsia, and bulimia of saccharine diabetes; it is not characterized by emaciation or by obesity; and, so far as yet appears, is unattended with special liability to pyogenic and other infections or with the risk of acid intoxication. Of its possible association with definite tissue changes or circulatory disturbances nothing is known.

Urinary dextrose is optically active; as the name implies, it rotates the polarized ray to the right. Being a reducing aldose, it is commonly recognized by its power to precipitate metals or their oxides from solutions of metallic salts, especially those of copper and bismuth when heated with an alkali. It is fermentable with

[1] Read at a meeting of the College of Physicians of Philadelphia, May 5, 1909.

yeast. These properties are manifested by the hexoses in general, as well as by the disaccharids—for example, sucrose and maltose—which contain twelve carbon atoms and may, by the hydrolyzing action of dilute mineral acids, be made to take up the elements of an additional molecule of water and separate into two hexose molecule groups. The pentoses are likewise reducing aldoses. They behave much like dextrose with the bismuth test of Boettger, but the reduction of metallic bismuth is usually incomplete and the precipitate is brown or gray, rather than an absolute black. With Fehling's solution, they give a peculiar reaction, producing somewhat suddenly, after some minutes' boiling, a heavy greenish or yellowish or orange-colored precipitate in place of the red or salmon-colored oxide with whose gradual development we are familiar. While decomposable by the action of certain bacteria, and especially the intestinal flora, they do not, however, ferment with yeast, and their bacterial decomposition is not attended with the evolution of gas. Consequently, in the examination of a specimen of urine which reduces bismuth imperfectly and gives an anomalous or incomplete copper reduction, the failure to ferment, more especially if polariscopic examination shows the reducing substance to be optically inactive, should direct attention to the possibility of the presence of a pentose. Diabetes mellitus is in such instances excluded; but other chemical tests must be made before the identity of the reducing, non-fermentable substance can satisfactorily be established. The most difficult discrimination is that between glycuronic acid and pentose. In the case which I report herewith I availed myself of the chemical skill and knowledge of Professor Charles H. La Wall to make this discrimination, and he has kindly consented to report the results of his tests and to explain their significance. While optical inactivity is almost conclusive, both against dextrorotatory glucose and levorotatory glycuronates, it must not be forgotten that many of the pentoses are optically active; and at least one of these has been known to appear in the urine. The crucial test is the recognition of the melting point of the crystals of pentosazone produced by the action of phenylhydrazin. Spectroscopic examination, moreover, shows different positions of the absorption bands of the substances produced by the action of various reagents with glycuronic acid, dextrose, and the pentoses.

The pentose group of saccharids—or, more correctly, a group of anhydrides, called pentosans, which bear the same relation to the pentoses that starch, for example, bears to dextrose—is widely distributed, if not universally present, in the vegetable kingdom; being found in fruits, leaves, stems, and roots. The legumens and, among fruits, the pear, are especially rich in pentosans. The nucleinic acid of the embryos of wheat was found by Osborne and Harris to contain three molecules of pentose to each 4 atoms of phosphorus. Pentose has been demonstrated by Kossel and

Neuman in the nucleinic acid of yeast, and Bendix, as well as Aronson, has found it in bacteria, including pathogenic forms, as tubercle and diphtheria bacilli. The most common forms of vegetable pentose are those termed l-arabinose and l-xylose. In the animal body, pentose was first discovered by Hammersten as a constituent of the nucleoproteid of the pancreas. The substance thus discovered has been identified as l-xylose. Since then various observers have demonstrated its presence in the liver, the thymus, the thyroid, the spleen, the kidney, the muscles, the brain, and the mammary gland, and it is, in general, supposed to be a persistent constituent of the nucleus; so that it is most abundant in those tissues that are rich in nuclei. Nevertheless, the whole amount contained in an ordinary adult human body has been calculated as not more than about 10 grams.

Pure pentose, when given to man or the carnivora by the mouth or injected into the blood, may be in small part assimilated; but it is usually, for the most part, rapidly excreted in unaltered form in the urine. Nevertheless, large quantities of pancreas or of vegetable foods containing pentosans may be ingested without the production of an alimentary pentosuria; probably on account of the slowness with which the saccharid is set free from its proteid combinations. The discordant results obtained by various observers in regard to the quantities of pentose recoverable from the feces and urine when pure xylose or pure arabinose has been administered by the mouth, are to be attributed in some measure to its decomposition, with the formation of lactic acid and alcohol, by the intestinal bacteria; and this process probably tends also to prevent alimentary pentosuria under ordinary conditions. While the pentosans and pentoses seem to play an important part in the nutrition of herbivora, no animal or vegetable enzyme that will hydrolyze pentosans has been demonstrated with certainty; and the physiological questions concerning their assimilation and utilization are as yet quite unsettled.

When alimentary pentosuria is induced by the feeding of pure pentose, the form that appears in the urine is the dextrorotatory l-arabinose,[2] whereas that which appears in essential pentosuria is the optically inactive r-arabinose. The apparent exception reported by Luzzato is attributed by some critics to a transient alimentary pentosuria accompanying the essential form. Urinary pentose is supposed to be excreted in combination with urea, as an arabinoseureid. To this fact is to be attributed the slow reduction giving rise to the peculiar reaction with Fehling's solution; for the

[2] The letters *d*- and *l*-, as prefixed to the names of the various pentoses, are as likely to be confusing to other physicians who do not happen to be expert chemists, as they were to me until I learned the facts. One would naturally suppose that *d*-arabinose is dextrorotatory and that *l*-arabinose is levorotatory; but the exact contrary is the case. The letters do not indicate the optical activity of arabinose, xylose, etc., but that of the hexose molecules with which the pentoses are respectively chemically homologous.

sugar must first be set free from its proteid combination by the action of the heat and alkali; and this decomposition occurs only after some minutes' boiling. In fact, in the first examination of the specimen from my own case I was unable to get any response to Fehling's test until I had added a decided excess of alkali.

Pentosuria was first clinically recognized in 1892 by Salkowski and Jastrowitz. The patient happened to be a person addicted to morphine, and his drug habit was supposed to have some causal connection with the condition. This idea, however, has been disproved. In 1895 Blumenthal reported two additional cases from Salkowski's laboratory. Since then a number of cases have been reported, most of them, however, from the First Medical Clinic in Berlin and Salkowski's laboratory. Neuberg identified the urinary pentose as r- or racemic arabinose, which is optically inactive, but may be decomposed into dextrorotatory and levorotatory constituents. Luzzato, however, found the pentosazone obtained from the urine of his patient to be slightly dextrorotatory, corresponding in this respect with the pentosazone of the l-arabinose of the vegetable kingdom. In my case a dextrorotation of scarcely 1° was found on one occasion only. The significance of this will be discussed later.

Three varieties of pentosuria have been recognized:[3] (1) *Alimentary pentosuria*, in which the phenomenon follows the ingestion of food rich in pentose-producing substances. (2) *Complicating pentosuria*, in which the urine contains both pentose and hexose—the cases being actually diabetes mellitus, and the small quantities of pentose transiently present having no known clinical significance. Similar to these cases are the instances of experimental pentosuria found to accompany the diabetes mellitus of dogs deprived of the pancreas or poisoned with phloridzin. (3) *Essential pentosuria*, in which the excretion of pentose is persistent, independent of diet, and not associated with diabetes mellitus. It cannot be said, nevertheless, that in essential pentosuria there is no association with hexosuria. The relation, however, is the reverse of that obtaining in complicating pentosuria. It is now the dextrose that appears transiently and in minute quantities, and even this has been recorded in but a few cases, of which my own appears to be one.

According to T. C. Janeway,[4] who, in 1906, reported two cases of essential pentosuria in brothers, there had been previous to his report but seventeen indubitable cases placed upon record, of

[3] The substance obtained by Cammidge from the urine of patients having pancreatic disease is also supposed to be a pentose. In a recent case of my own showing a slight Cammidge reaction glucose was excreted for a few days; and then a reducing, non-fermentable substance, not yet identified. A similar series of phenomena occurred in the case of an obese woman of diabetic and carcinomatous heredity, and marked vasomotor ataxia of the menstrual variety; suggesting a possible origin in pancreatic circulatory disturbance. This case is reported in my paper on "Visceral Angioneuroses," in the Transactions of the Association of American Physicians, 1909.

[4] Amer. Jour. Med. Sci., 1906, cxxxii, 423

which one came from Italy and two from Norway, but none had been found in British, French, or American literature. So far as I know, the present is the fourth case observed, and the third case to be placed upon record, in the United States. Added to the seventeen cases collected by Janeway, with the two reported, and two others (unpublished) alluded to by this author, it would make twenty-two in all. I have not searched the literature since Janeway's report, and there may be a few more. At all events, the total number of cases recorded in the seventeen years elapsing since the first clinical recognition of the condition, has not reached forty. For this reason, isolated cases are still worthy of report.

My patient is a married man, a native of one of the middle Western States, aged fifty years. He has never had any venereal infection. He uses alcohol rarely and tobacco moderately. He is a leading member of the bar of his State, and is frequently required to appear in the supreme courts of other States and of the United States. It may, therefore, fairly be said that he has been engaged for many years in arduous, sometimes exhausting, mental labor; and, if we consider the strain of travel and of pleading, in physical labor as well. However, he has the vacation habit well established, and except for an occasional European trip, usually spends his summers in the woods or mountains, or on the Maine Coast, tramping, boating, fishing, hunting, or loafing, as the environment and his mood may suggest. When at home he rides and golfs as opportunity offers. He does not, therefore, strictly speaking, lead a sedentary life. He has recently—that is to say, for some four or five years past—been actively engaged in a movement for reform in the government of his city; and has had in connection therewith the burden of preparing important legal cases against a number of eminently respectable citizens. It is to be supposed, therefore, that he has been under a severe mental strain.

While he exhibits some of the signs of vasomotor ataxia, he is not what is commonly termed neuropathic; and there is not in his family any history of neuropathic, arthritic, malignant, tuberculous, or diabetic affection. Cutaneous affections have been present.

He first came under my care about fifteen years ago with symptoms of subacid, gastro-enteric indigestion. Recovery took place under lavage, gastric faradization, and regulation of diet and exercise. The urine showed an excess of indican, as well as of uric acid, urates, and oxalates, but contained no albumin, sugar, or casts. An attack of furunculosis some years later made me study the urine carefully and persistently for glucose, but none was found. The patient has had from time to time brief periods of indigestion, sometimes a transitory constipation; but there has been no significant ailment of any kind. He has had periods of genuine and well-earned fatigue, but no neurasthenia. He has seen me at least once in every year, often more frequently; and I have probably examined his urine three or four times in each

year, finding neither albumin nor sugar. He has also consulted, when necessary, a leading physician of his home city, one of my own pupils, whom I have associated with me in the case. It is unlikely, therefore, that any pathological occurrence would go long unnoticed.

In March, 1908, a life insurance examiner postponed his application, and he learned indirectly that it was on account of the urinalysis—albumin was said to be present. There was no suspicion, apparently, of sugar. The local physician examined the urine and found no albumin, but an anomalous reduction with Fehling's solution. He suggested that diabetes might be impending, but in the total absence of symptoms hesitated to make the diagnosis. A specimen of urine, taken from a twenty-four-hour collection amounting to 1500 c.c., was sent to Philadelphia. I found it to be clear, amber in color, 1023 specific gravity, acid in reaction, giving a brownish precipitate with bismuth subnitrate and potassium hydroxide, a greenish-yellow precipitate with Fehling's solution, and no gas upon attempted fermentation with yeast in Einhorn's saccharometer. There was no albumin; casts were not detected. A few leukocytes formed the only microscopic finding. Suspecting pentose, I enlisted Professor La Wall's cooperation, and, studying the specimen with him, found it to give all the pentose reactions, but in exception to be slightly dextrorotatory. A few days later the patient himself arrived. Careful physical examination showed nothing abnormal except a very slight enlargement of hepatic dulness, which had been present for some four or five years, and a very slightly increased arterial tension, not high enough, however, to indicate pathological change in the arteries. The blood was normal to microscopic and color study. The eyeground had been examined by a local oculist, and was reported to be normal. The patient had gained some twenty pounds in weight during the last five years, but was not pathologically obese.

I have, in conjunction with Mr. La Wall and the local physician, kept the patient and the urine under observation, more or less closely, ever since; that is to say, for more than a year. Twice during that time he has complained of lassitude and indisposition to work—symptoms quickly disappearing after a few days at Atlantic City, or the brief administration of lecithin or glycerophosphates. Milk diet, flesh diet, diet with and without the ordinary carbohydrates, and diet with and without substances rich in pentosans have been instituted; for brief periods only, it is true, as the patient's activity does not lend itself to overmuch regulation or restriction. There has been practically no change in the urinary findings, except that although Mr. La Wall has not again found any dextrorotation, the local physician in February of this year did find, on one occasion, a few bubbles of gas; and on another, a reading of 0.25 per cent. by gaseous column, in Einhorn's saccharometer. I did not have either of the specimens, and cannot

confirm the observation; but I know the observer to be accurate. This would seem to indicate some transient complicating excretion of a fermentable sugar [and, since the paper was read, a small quantity of hexose has again been found, as set forth in the footnote].

There is no instance on record of the transformation of pentosuria into diabetes, yet while knowledge remains so limited, care is necessary. I therefore thought it well to test dextrose assimilation more particularly. For this purpose I gave the patient, by the mouth, on each of two successive days, 100 grams of the glucose of pharmacy, in two portions; and with Mr. La Wall examined the total urine of the forty-eight hours. In this there was no trace of any excreted hexose, but pentose was found as before. No excess of indican has been found in the pentose-containing urine, although this was occasionally present before the pentosuria was discovered. The excretion of urea continues around 3 per cent. The chlorides in the late specimen were 0.94 per cent., or about 15.46 grams. The phosphates, estimated as P_2O_5, were 0.3 per cent., or 4.8 grams, a slight increase over the normal average. The total sulphates, being 0.31 per cent., or 5 grams, of which 0.3 per cent. represents preformed salts, show also a slight increase; while the rather low ratio of conjugate to fixed sulphates, 1 to 30, especially when taken in connection with the low indican content, would show a relative absence of intestinal decomposition. Bacterial study of the feces is therefore desirable, for a question is raised as to the possibility of absence or partial destruction of intestinal bacteria as a factor in the production of the pentosuria. Whether or not this study can be carried out, I do not know, but it calls for attention. The salol test does not indicate any failure of the secretion that splits this drug.

I have not specially experimented with the feeding of sucrose, levulose, lactose, etc., or with any pure pentose; but hope to have the opportunity to make these and other observations from time to time, as the patient finds opportunity to visit Philadelphia, or we succeed in enlisting expert chemical assistance in his own city.[5]

The diagnosis of essential pentosuria is established by the persistence of the pentose excretion and by the absence of other symptoms.

The chief importance of this condition at present, apart from the

[5] Our patient, however, informs me that I have "overestimated his zeal for scientific research." He consented, nevertheless, to visit Berlin while in Europe this summer, and to see Dr. Jastrowitz, who writes as follows:

"Both Professor Salkowski and I, can, from careful studies, entirely independent of one another, confirm your diagnosis of pentosuria. The first time that the patient brought his urine to me, I found, in addition to pentose, $\frac{1}{2}$ per cent. of hexose, but although I had the urine of various periods brought to me later, as well as the entire twenty-four hours' quantity after diets rich in carbohydrates, I could not find any increase of hexose, but, on the contrary, only occasional traces of it; nor did the pentose seem to be notably increased after he had eaten many cherries (kirschen)."

interesting questions in physiological chemistry to which it gives rise, is its liability to be mistaken for diabetes mellitus, or, at all events, for glycosuria. Indeed, most of the cases hitherto recorded have been so mistaken until coming under the care of a physician familiar with the fact that pentose may appear in the urine, when the diagnosis has been corrected.

Pentosuria is apparently an intractable condition, but occasions very little inconvenience, and, so far as yet appears, is devoid of danger to life. About the worst thing that can happen to the patient is to have the condition mistaken for glycosuria and to be restricted in diet accordingly. This is very likely to cause loss of strength as well as of flesh. When, however, the true nature of the case is recognized and a diet properly adapted to the individual conditions instituted, the patient rapidly recovers from this loss and appears to be normal in every respect, except for the urinary findings. The only medicament which, from report, seems to influence the condition favorably, is arsenic. In the case of my own patient no medication has as yet been employed.

No light is thrown upon the metabolic fault concerned in the production of pentosuria by the habits, age, sex, vocation, nationality, or social and climatic environments of the patients as thus far recorded. Their ages vary from twenty to sixty-five years; they are of both sexes (although at first only males were reported), and their occupations, birthplaces, and environments have been as little similar as banking and farming; idling and practising law; wealth and poverty; Germany, Norway, Italy, and the Eastern and middle Western regions of the United States. Some of them have been morphine takers, some cocaine users, some neurasthenics. Two have been vegetarians. Quite a few cases have been observed in brothers, or in sisters, or in brother and sister; so that there seems to be some indication of a family tendency.

As the pentose continues to be excreted, even when the patients are put upon exclusive milk diet, and rarely seems to be increased notably, even by a diet of pancreas or pears, it is somewhat difficult to attribute the excretion of pentose to failure in assimilation of foodstuffs. The theory that pentosuria results from the breaking up of the pentose-proteid combinations of the body tissues has in its favor the discovery of arabinose in the blood of one or two patients; but against it, on the other hand, is the fact that the body pentose is l-xylose and the urinary pentose r-arabinose. Granting, however, that transformation of these isomers could be explained if we knew the intimate mechanism of the metabolic failure, there remains the still greater difficulty that the average daily urinary excretion in the cases thus far observed has been from 5 to 20 grams of pentose, whereas the entire body contains but about 10 grams. The problem, therefore, still awaits solution.

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THE CHEMICAL EXAMINATION OF A SAMPLE OF URINE CONTAINING PENTOSE.[1]

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The urine, which had a specific gravity of 1023 and a yellow color, first attracted attention by the abnormal reaction produced when heated with Fehling's solution, which was not reduced to copper oxide, as is the case when the ordinary carbohydrates are present, but which produced a characteristic greenish turbidity and eventually a yellow precipitate. The fermentation test gave negative results, while a pronounced reduction was obtained by means of Boettger's test with bismuth subnitrate and solution of potassium hydroxide. A more extended examination, therefore, seemed desirable, and about a pint of the urine was furnished, with a request for an exhaustive investigation.

The first test applied was the alphanaphthol test, which is a group test for carbohydrates in general. It is applied by adding to a suspected sample of urine a few drops of a 10 per cent. alcoholic solution of alphanaphthol and then superimposing this liquid upon concentrated sulphuric acid. In the presence of any carbohydrate a violet zone is produced. This test resulted positively.

The Fehling test was then applied, with the result as previously stated. The reaction showed a greenish turbidity, which was succeeded by a yellowish precipitate, wholly unlike the normal copper reduction.

The Boettger test, with bismuth subnitrate and solution of potassium hydroxide, showed a marked reduction to the dark-colored metallic bismuth.

The indigo carmine test for dextrose gave negative results.

A fermentation tube showed no evolution of CO_2 after twenty-four hours.

A polariscopic examination of the sample showed that it was optically inactive.

[1] Read at a meeting of the College of Physicians of Philadelphia, May 5, 1909.

The phenylhydrazine test was then applied as follows: A clean, dry, six-inch test-tube was filled to the depth of one-half inch with phenylhydrazine hydrochloride, one-half inch of dried sodium acetate was added, and the tube filled to half its capacity with the urine and immersed in a bath of boiling water for two hours. Upon cooling the contents of the tube a voluminous deposit of yellow crystals took place, which, when examined microscopically, were found to be in stellate tufts of acicular crystals, resembling somewhat the groups produced by dextrose or levulose, but different in the character of the individual crystals, which seemed to be more slender in proportion to their length.

Several additional tubes of the crystals were prepared in a similar manner, and some of the crystals were collected and purified by recrystallization. During this purification it was noticed that the crystals were much more soluble in hot water than is the case with ordinary dextrosazone. The purified crystals were found to have a melting point of 157° C. This corresponds closely to the melting point of pentosazone; which substance was found by Salkowski and Jastrowitz to have a melting point of 166° to 168° C. when pure, but from 156° to 160° C. when obtained from urine. The melting point of dextrosazone (and levulosazone) is 204° to 205° C.

Several subsequent experiments upon fresh samples of material confirmed the melting point of the crystals, and the various specific tests for pentose were applied. Tollen's test, which is carried out by heating a solution of phloroglucin in hydrochloric acid and adding to the hot solution a small quantity of the urine, continuing the heat upon a water bath for some time, gave positive results in the shape of a cherry-red liquid which became cloudy upon cooling.

As glycuronic acid also responds to this test, further confirmation was obtained by applying the orcin-hydrochloric acid test, which is carried out similarly to the one previously described, using orcin instead of phloroglucin. In the presence of pentose a bluish-green color is developed, which is dissolved out by shaking with amyl alcohol. Positive results being obtained by this test, thus negativing the presence of glycuronic acid, there seems to be no further doubt that there is exhibited in this sample of urine a well-developed case of pentosuria, as precisely the same results as above described were obtained in a specimen of urine from the same individual examined eleven months after the first report.